Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Raring for change
Confluence of scientific discovery and advocate alignment warrants vital new investments in The Epilepsies

1. The Epilepsies' landscape has dramatically changed

In the past two decades, our understanding of epilepsy has evolved from a single disease to a multitude of syndromes.[1] Simultaneously, advances in basic science, neuroimaging, and especially genetic sequencing are accelerating rare epilepsy diagnoses. A rare epilepsy is a disorder or syndrome affecting fewer than 200,000 Americans that is defined by a particular cause, certain type of seizure(s), and a specific constellation of symptoms or comorbidities.[2] Current incidence and prevalence of the rare epilepsies by seizure type and/or etiology are largely unknown.[3] Meanwhile, social media and technology developments are bridging the gaps between disparately located patients with rare epilepsy and their families and contributing to the founding of rare epilepsy disease focused 501c3 nonprofit organizations and support groups (collective referred to hereinafter as Rares).[4] Concurrently, interest in precision treatments using both drugs and devices targeting rare epilepsies is intensifying.[5] Despite these intersecting developments, there are still no standardized clinical guidelines for many rare epilepsy syndromes, no curative treatments other than surgery in a very few diagnoses, few treatments to reduce seizure frequency or improve developmental outcomes and quality of life, and no centralized method for identifying individuals with rare epilepsies to improve surveillance, understanding of population, or to conduct comparative effectiveness research. The Epilepsies' landscape dramatically changed over the past two decades. However, a thorough scan of the evolving rare epilepsy diagnoses, their respective organizations, and their impact on the ecosystem at large was missing.

The Rare Epilepsy Landscape Analysis (RELA)[6] was conceived to take stock of the emerging rare epilepsy ecosystem and to empower leaders of the ever-expanding number of organizations representing individuals with rare epilepsies and other epilepsy stakeholders to be more strategic in the utilization of scarce dollars, people, and resources. The RELA was an outgrowth of the Rare Epilepsy Network (REN)[7] — originally a Patient-Centered Outcomes Research Institute (PCORI)-funded rare epilepsy registry that collected patient and caregiver data from 2013 to 2018 for 1459 participants across 41 epilepsy-related syndromes to better understand the conditions, accelerate treatments, and improve the lives and quality of care of people living with them. A summary of the organizations that participated in the REN registry and the number of participants for which data were collected can be

[1] Institute of Medicine (IOM). Epilepsy Across the Spectrum: Promoting Health and Understanding. The National Academies Press; Washington, DC: 2012, https://www.ncbi.nlm.nih.gov/books/NBK91506/pdf/Bookshelf_NBK91506.pdf.

[2] A rare or orphan disorder is a disease or condition that affects fewer than 200,000 Americans. There are more than 7000 known rare diseases affecting more than 25–30 million Americans. One in 10 Americans are living with a rare disease, and children represent the vast majority of those afflicted. Eighty percent of rare diseases are not acquired but inherited by mutation or gene defect. Rare diseases are characterized by a wide diversity of symptoms that not only vary disease to disease but also among patients with the same diagnosis. Rare diseases impact the person diagnosed, as well as families, friends, health providers, and society at large. https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases [accessed June 18, 2020].

[3] Neurology® 2017;88:296–303. N.Tian, J.B. Croft, R. Kobau, et al., CDC-supported epilepsy surveillance and epidemiologic studies: A review of progress since 1994, Epilepsy & Behavior, https://doi.org/10.1016/j.yebeh.2020.107123.

[4] Rare epilepsy organizations (Rares) range from traditional 501c3 nonprofits to more informally organized support groups on Facebook or via list-serve networks.

[5] Auvin S, Avbersek A, Bast T, et al. Drug Development for Rare Pediatric Epilepsies: Current State and Future Directions. *Drugs*. 2019;79(18):1917–1935. doi:https://doi.org/10.1007/s40265-019-01223-9.

[6] The project included interviews with Rare Epilepsy Network (REN), Rare & Catastrophic Seizure of Childhood (RCSC), Epilepsy Foundation (EF), Epilepsy Leadership Council (ELC), American Epilepsy Society (AES), National Institute for Neurological Disorders & Stroke (NINDS), National Organization for Rare Diseases (NORD), Citizens United for Research in Epilepsy (CURE), Child Neurology Foundation (CNF), Centers for Disease Control (CDC), and leaders of individual rare epilepsy organizations. Outreach resulted in the identification of 75 rare epilepsy-focused organizations and support groups. A volunteer advisory committee comprised of rare epilepsy organization leaders including Brittany McLarney (Phelan-McDermid Syndrome Foundation); Jo Anne Nakagawa (TS Alliance); Maryanne Meskis (Dravet Foundation); Amber Freed (Slc6a1 Connect); Heidi Grabenstatter (International Foundation for CDKL5 Research); JayEtta Hecker (Wishes for Elliott & DEE-P Connections); Shelley Frappier (The Cute Syndrome), and Geraldine Bliss (Cure Shank) helped develop and test a ten-part 111-question survey covering background, founding, disease impact, patient/caregiver information, research, professional education, advocacy and awareness, management and operations, resources and financials, and fundraising. The survey was built in Qualtrics, and 44 complete responses were received.

[7] The REN Registry was a collaboration led by Epilepsy Foundation, Columbia University, and Research Triangle Institute (RTI) in collaboration with 32 rare epilepsy organizations. A complete list of participating rare epilepsy organizations can be found at https://efa.rexdb.net/anon/site/anon/additional-information [accessed June 18, 2020].

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found in Table 1.[8] Through the REN registry and affiliated network, Rares observed an abundance of commonalities shared across epilepsy syndromes.[9] Beyond the registry, the REN emerged as a place where groups exchanged information, strategies, and expertise and could learn from one another in their efforts to make change for lived experience of persons with epilepsy. The evolution of the REN over five years made clear that a detailed profile of the ever-expanding number of organizations and their activities was needed to understand the breadth of the community, the depth of their resources and expertise, and opportunities for expanded collaboration, coordination, and efficiencies.

While unforeseen at the time, this snapshot of the rare epilepsy landscape is even more timely in light of the 2020 COVID19 Pandemic, which has forever altered the landscape for health and care in the United States and around the world. The RELA provides a current snapshot of the pre-COVID19 Rare landscape. Rare epilepsy organizations are experiencing higher demands for their programs and services. However, key revenue-generating events needed to support these efforts are in jeopardy, and there is widespread concern that it could take years to return to pre-COVID19 revenue levels, if at all. Resourceful by necessity, time will tell which Rares have the capacity to adapt to the changed times and survive. Simultaneously, medical research especially on rare diseases has been put on hold as some labs are closed, operating at low capacity, or have switched focus to coronavirus.[10] The impact on rare epilepsy research, development of novel interventions and translation to rare patients with epilepsy will be felt for years to come. COVID19 has taught us in many ways that our survival depends on acting communally. In a world reshaped by COVID19, it is likely that individual Rares will be even more dependent on collaboration and coordination across shared interests.

Table 1
Rare Epilepsy Network (REN) registry by rare syndrome and number of patients participating in the registry.

Syndrome	No.	Syndrome	No.
Aicardi syndrome	100	Ohtahara syndrome	18
Angelman syndrome	5	PCDH19 female epilepsy	41
Batten disease	3	Phelan–McDermid syndrome	43
CDKL5 disorder	32	Progressive myoclonic epilepsy (PME)	8
Congenital bilateral perisylvian syndrome	2	RAS pathway disorders	1
CSWS/ESES	17	Rasmussen's encephalopathy	5
Doose syndrome	76	Rett syndrome	1
Dravet syndrome	177	Ring 14 syndrome	8
Dup15q syndrome	62	Ring 20 syndrome	4
Early myoclonic encephalopathy	1	Severe myoclonic epilepsy of infancy	7
Glut1 deficiency	4	SCN2A mutation	4
Hypothalamic hamartomas	91	SCN8A mutation	25
Infantile spasms/West syndrome	67	SLC13A5 mutation	3
Jeavon's syndrome	9	Sturge Weber syndrome	1
KCNQ2 mutation	9	SYNGAP1 mutation	18
Landau–Kleffner syndrome	10	Tuberous sclerosis complex	256
Lennox–Gastaut syndrome	207	Unverricht-Lundborg syndrome	3
Lissencephaly	4	Encephalopathy with seizures and major delay in development	23
MERFF	3	Other mutation associated with seizures	110
Mitochondrial disorders (Alper's disease, Leigh's disease)	1	Total	1459

2. Common challenges emerge across the rare epilepsies

The full texts of the RELA[11] & Appendix[12] include insights into the Rares collectively and individually. This first-of-its-kind effort cataloged the founding, mission, organization, staffing, research funding, infrastructure, and assets across 44 responding organizations.[13]

Broadly, the survey showed an explosive growth in the number of Rares in the last decade. Twenty-seven Rares were founded since 2010 — five were founded in 2019 and more continue to emerge. Most organizations were founded by parents of children with rare conditions. They were motivated by a lack of information, community, treatments, and research for the condition. Nearly half of the organizations relied exclusively on volunteers with no paid staff to operate and deliver programs and services. While the majority surveyed were headquartered in the United States, many served global constituencies given the international demand for information and programs. Priorities and challenges were explored across five domains including the following: (1) information and support, (2) research, (3) professional education, (4) advocacy, and (5) fundraising. The following three common themes emerged from the analysis.

2.1. Small, disparate patient populations have difficulty connecting with specialized multidisciplinary care

One of the highest priorities reported across the Rares was connecting individuals with epilepsy with specialists across multiple medical disciplines. The Rares were aligned in their urgency for the clinical and research communities to recognize the multimodal nature of these conditions. Rares consistently reported challenges in obtaining early and accurate diagnosis. They described the tremendous diversity in diagnosis, treatment, and management across and even within medical centers. Further, they prioritized developing and disseminating best clinical practices and guidelines. The challenges preventing the execution of these priorities included educating disparate professionals from multiple specialties. They also described an unwillingness for some healthcare providers and specialists to learn beyond the scope of their practice focus. Rares expressed concern over a lack of professional collaboration among physicians as well as institutional territorial behaviors between centers. Because of the inherent nature of Rares being rare, treating such small numbers of disparate, geographically dispersed patients compounds the problems of ensuring specialized, expert support across a broad spectrum of patient experiences and outcomes within each disease. Ensuring that individuals get expeditious access to knowledgeable, up-to-date, multidisciplinary healthcare providers and interventions steeped in best practices is a pervasive challenge across the majority of rare epilepsy diagnoses.

[8] [dataset] Rare Epilepsy Network [accessed March 30, 2020] No. represents the number of participants per organization. MERFF stands for myoclonic epilepsy with ragged red fibers. Epileptic encephalopathy with continuous spike and wave during sleep is abbreviated to CSWS and electrical status epilepticus during slow sleep is abbreviated to ESES. The table reflects the organizations; therefore, there may be some overlaps for numeric counts in subgrouping of syndromes e.g., ESES and LGS, which may both qualify as Lennox–Gastaut.

[9] The data covering 12 domains including affected person demographics and family history, caregiver demographics, lifestyle and quality of life, seizure characteristics, diagnostic history, development and phenotypic characteristics, comorbidities, development, and treatments are available at: https://efa.rexdb.net/anon/site/anon/hom [accessed June 18, 2020]. Instructions and requests for REN data transfers can be obtained https://www.epilepsy.com/sites/core/files/atoms/files/REN_Data_Request_proposalCENTRAL%20%20Process_LS_PK_kf%20-%20ls%20edits%204-8-20.pdf [accessed June 18, 2020].

[10] https://www.washingtonpost.com/health/the-coronavirus-pandemic-claims-another-victim-medical-research-for-deadly-rare-diseases/2020/06/03/2a65c10a-947e-11ea-91d7-cf4423d47683_story.html.

[11] The Rare Epilepsy Landscape Analysis (https://www.epilepsy.com/sites/core/files/atoms/files/RARE%20EPILEPSY%20LANDSCAPE%20ANALYSIS%20-%20FINAL%20DISSEMINATION.pdf) is a 31-page analysis that includes responses from 44 individual Rare organizations. The RELA and Appendix were disseminated in January 2020 to RELA survey responders and other stakeholders. Additional insights from the underlying survey responses may be requested from the author.

[12] The analysis is accompanied by a 38-page Appendix (https://www.epilepsy.com/sites/core/files/atoms/files/RARE%20EPILEPSY%20LANDSCAPE%20ANALYSIS%20APPENDIX-%20FINAL%20DISSEMINATION.pdf) with verbatim insights from Rare leaders.

[13] A complete list of the 75 rare epilepsy organization invitees and 44 responders is included in the analysis. Broadly, it included organizations founded from 1974 through 2019 geographically dispersed across the US. Many of the responding organizations represented genetic epilepsies, while others included lesions, rings, or other manifestations. Forty-three out of the 44 responders consented to be included in the Appendix, which includes stories, quotes, and other verbatim insights.

2.2. The toll of rare epilepsies is unknown, as is the natural history of many diseases

The reported incidence and prevalence across the different rare epilepsies were highly variable and difficult to collect and analyze. Only 13 organizations reported statistics for international incidence. For those, incidence ranged from more common, and yet still rare syndromes like tuberous sclerosis complex with a 166/1 million incidence to conditions like Ring14, cardio-facio cutaneous syndrome (CFC), and LaFora Syndrome each reporting incidence of 1/1 million. For prevalence, only 17 organizations reported international prevalence statistics. Frequently, organizations explained that prevalence and incidence were largely unknown, outdated, and/or at best estimates.

In regard to registries, twenty-five organizations reported having patient contact registries, some that dated back to 1989. The information was housed in universities and foundations like the National Organization for Rare Disorders (NORD) and Simons Searchlight. Organizations have enrolled from 25 to 5000 individuals, and the registries are funded primarily by individual donations with costs ranging from $1000 to $10,000 annually to maintain. The high value of these registries resides in the collection of phenotype and genotype data to characterize the disease, recruitment to clinical studies and trials, and identification of prevalence, trends, and life course of the syndrome. However, some organizations reported that they were not using their contact registry or are not sure how to use it most effectively. At least seven organizations expressed concern that the cost of maintaining the contact registry was not sustainable.

Similarly, twenty organizations reported natural history registries dating back to 2006 through the present. These were also housed in universities and some foundations. They included enrollees from as few as 20 to as many as 2200 and ranged in cost from $3500 to upwards of $5 million annually. Some were funded by Food & Drug Administration (FDA)/National Organization for Rare Disorders (NORD), National Institutes of Health (NIH), foundation grants, industry, and individual donations. Several Rares expressed concern about the sustainability of these registries despite their value for tracking seizure outcomes, supporting drug company applications to FDA for clinical trials, and marrying clinical data with biosamples to foster and support research on disease mechanisms. Taken together, what emerged is a lack of understanding of the overarching burden of rare epilepsy diagnoses on patients, their families, communities, and healthcare systems. Moreover, there is a complex and costly landscape of disconnected registries of varying sizes across many diseases despite commonalities in elements and goals.

2.3. Research funding is not commensurate with research promise in rare epilepsies

Of the 44 organizations surveyed, 38 reported a known gene, ring[14] or deletion[15], yet none of those diseases have any cures. A small number of the diseases[16] relied on diet, devices, and/or surgery to eliminate seizures. The cure rates for seizures for these conditions varied significantly and typically did not improve comorbidities or overall quality of life. Thirty rare organizations reported a history of funding research; however, they described primarily funding single projects to push pathways for cures forward.[17] For the 17 organizations who reported funding research in their last fiscal year, they collectively invested $3.6 million in research for FY2018.[18] The Rare investment coupled with Epilepsy Foundation's (EF) $3 million investment[19] and Citizens United for Research in Epilepsy's (CURE) $3.2 million investment[20] amounted to less than $10 million combined annual private research investment. Only a few organizations reported having received NIH, Department of Defense, or other federal grants. The survey did not measure federal or private research funding to researchers and academic institutions by each rare disease — a query that should be addressed in future surveys. In FY19, NIH funded $188 million for epilepsy of which $129 million came from NINDS. There were 503 grants coded for epilepsy across 22 institutes.[21] However, grants are not coded for rare versus common forms of epilepsy so at this time, parsing out that specific information is difficult. Moreover, the ICARE Epilepsy Research Portfolio Analysis (April 2019) of epilepsy research across NIH Institutes for 2013–2017 reported that most federally funded epilepsy research is not specified to syndromes.[22] Further, until 2020, no Rare responders reported receiving money from prominent health foundations, e.g., Gates.[23] This trend changed for the better in 2020 when seven Rares were awarded two-year $450K grants from the Chan Zuckerberg Institute (CZI) to develop infrastructure to expedite research and discovery.

The Rares collectively reported their highest priorities were developing natural history registries, understanding the mechanisms of their diseases, and funding translational science. Their biggest challenges were connecting researchers to seed collaborations, accessing funding, and acquiring sufficient patient data for clinical trials. The inference here is that while research advances have led to mechanistic understanding of some rare epilepsies, that must now be translated into better treatment and cures. And more research is needed to increase our mechanistic understanding of the majority of diseases that are understood "just a little" or "not at all." Moreover, historically interventions have focused on the seizure cessation, even though many patients advocate that the comorbidities are often more debilitating than the seizures themselves. Research into comorbidities and cures or interventions to minimize their significant effects is long overdue. The priorities and challenges identified by the Rares strongly suggest that there is a disconnect between the research promise, the needs of patients, and the resources available to accelerate research across the Rares.

3. Consensus around high priority collaborations across Rares

Not only was there alignment around challenges, but when asked to identify opportunities for collective action on high priority initiatives, the response from Rares' reflected tremendous consensus. The specific tactics to implement the goals below would require discussion, debate, and consensus across many broad stakeholders. Transforming care, improving disease understanding, increasing research, and translating interventions have broad support across the Rares.

[14] A ring is a chromosome abnormality caused by the fusion of two arms of a straight chromosome during prenatal development.

[15] A deletion is a chromosomal abnormality in which a portion of the gene is missing.

[16] Hypothalamic hamartomas reported a cure rate of 51–75%. SLC13A5 and ring chromosome 20 reported cure rates of 1–5%.

[17] This finding is corroborated by the ICARE Epilepsy Research Portfolio Analysis (April 2019) slide 8 and 10 that report nonprofit funding in epilepsy research is weighted to clinical research including clinical outcomes, early detection, and treatment. https://www.ninds.nih.gov/sites/default/files/icareportfolioanalysis_presentation2019_508c.pdf [accessed June 17, 2020].

[18] $2.4M of the total was invested by Tuberous Sclerosis Alliance.

[19] Epilepsy Foundation, Action Together, Annual Report FYI8, https://www.epilepsy.com/sites/core/files/atoms/files/AR%20FY18_Epilepsy%20Foundation_FINAL.pdf [accessed June 18, 2020].

[20] Citizens United for Research in Epilepsy, Audited Financial Statements, Years Ended December 31, 2018, https://www.cureepilepsy.org/wp-content/uploads/2019/09/2018-CURE-AFS.pdf [accessed June 18, 2020].

[21] Email with NINDS staff (June 2019).

[22] ICARE Epilepsy Research Portfolio Analysis (April 2019) of federal and nonprofit funders from 2013 to 2017 in Slide 11 reported that most federally funded epilepsy research is not specified to one syndrome but weighted toward Epilepsy — not otherwise specified, temporal lobe epilepsy (TLE), posttraumatic epilepsy (PTE), seizures, seizures associated with other disorders (like Alzheimer's, autism, fragile X, malaria, status epilepticus, focal epilepsy, childhood epilepsy, epileptic encephalopathies, sudden unexpected death in epilepsy (SUDEP), malformations of cortical development, etc.) https://www.ninds.nih.gov/sites/default/files/icareportfolioanalysis_presentation2019_508c.pdf [accessed June 17, 2020].

[23] https://chanzuckerberg.com/newsroom/chan-zuckerberg-initiative-awards-13-5-million-to-drive-progress-against-rare-diseases/ [accessed June 18, 2020].

3.1. Launch strategic initiatives to improve quality of life, care and outcomes

A major shared challenge among Rares is ensuring their constituents get fast access to knowledgeable experts across multiple disciplines. Multiple recommendations were shared that would improve the quality of life, care, and outcomes for the individuals with epilepsy. Moreover, many of the recommendations could be implemented most cost and resource effectively across Rares. A few shared high-priority recommendations included the following:

- Establishing a national system of multidisciplinary clinics or Rare Epilepsies Centers of Excellence;
- Developing Quality of Life Scales that reliably measure meaningful outcomes for individuals with rare epilepsies and enable efficient, patient-centered clinical trials;
- Crafting and disseminating comprehensive yet disease-specific diagnostic, treatment, and management guidelines and/or best practices; and
- Educating multidisciplinary practitioners (e.g., pediatricians, geneticists, neuropsychologists, endocrinologists, nurses, and social workers) and newly trained healthcare providers (e.g., medical students, interns, fellows) on rare epilepsy diagnoses, treatment, management, and referrals.

It is time to explore these and other strategies to ensure all individuals with epilepsy including individuals with rare epilepsies are expeditiously diagnosed, referred to the highest level care, managed consistent with the best current practices, and obtain the best outcomes for both seizure control and quality of life possible. Moreover, successful models already exist within the rare epilepsy community (e.g., tuberous sclerosis complex) and other health communities (e.g., cancer) that can be drawn from, adapted, and scaled across Rares.

3.2. Establish a National Registry for The Epilepsies

As reported in the RELA, twenty contact and twenty-five natural history registries were reported by individual Rares, but they are largely disconnected, and data was not standardized across them. Some organizations are struggling to maintain them and others to fully utilize them. The REN was a huge leap forward in gathering information across 41 syndromes for key domains including seizures, comorbidities, and medications. While REN is a significant proof of concept for a collaborative rare registry and houses compelling individual and cross rare data, culturally, there exists a bias against patient reported data. There are some promising nationwide efforts afoot to improve clinically validated data collection in rare epilepsies including quality improvement networks such as the Epilepsy Learning Healthcare System (ELHS)[24] and the Pediatric Epilepsy Learning Healthcare System (PELHS).[25] Each of these systems provides valuable clinically validated population health data for The Epilepsies. To realize their full potential, these efforts require broad participation and collaboration across epilepsy clinics and sustainable long-term funding support. Additionally, examples of national, multistakeholder-funded natural history registry solutions exist that could be models for epilepsy. The National Neurological Conditions Surveillance System – a surveillance pilot for neurological conditions – is currently underway for multiple sclerosis (MS) and Parkinson's disease (PD) at the Centers for Disease Control (CDC). However, the pilot does not presently include The Epilepsies that are the 4th most common neurological disease with prevalence that supersedes MS and PD combined. In a recent publication, the CDC identified 15 surveillance or epidemiological research gaps in epilepsy and recommended surveying prevalence for children with epilepsy syndromes and a national epilepsy registry modeled after amyotrophic lateral sclerosis (ALS) or cancer among others.[26]

A coordinated, comprehensive national surveillance of The Epilepsies including etiologies is urgently needed. A national registry would help us quantify the burden of these complex, multifaceted diseases on individuals with epilepsy, families, and society. Moreover, unlike other diseases that primarily impact adults, The Epilepsies impact people of all ages from birth to death with a high prevalence among children and the elderly. The Epilepsies are complex, often impact multiple systems, and have tremendous variability even within each diagnosis making them hard to understand and treat without a comprehensive understanding. Moreover, 30–40% of individuals with epilepsy have uncontrolled seizures despite available treatments. The cost of uncontrolled seizures is 2–10 times higher than those with controlled seizures.[27] A lack of a comprehensive understanding of The Epilepsies results in poor outcomes for those impacted and their families. It also contributes to increased healthcare costs, loss of life, lack of productivity, and diminished quality of lives lived. Research efforts and progress will continue to be fundamentally impeded by the absence of comprehensive, longitudinal and compatible natural history data on the course of rare epilepsies, and the impact of treatments and other factors to optimize the clinical management of individuals with epilepsy, improve their quality of life, and advance the development of therapeutics.

3.3. Advance new paradigms and increase funding for epilepsy research ripe for investment

At the June 2020 Global Genes Rare Drug Development Symposium, Christopher P. Austin, M.D., Director of National Center for Advancing Translational Science (NCATS), explained "there is a growing discordance between known molecular basis of disease and the development of therapies across all 7000 rare diseases." Dr. Austin posited that the translation system is broken and without significant systemic change, it will take 2000 years for treatments to catch up to our molecular understanding of rare diseases. National Institute for Neurological Diseases and Stroke (NINDS) and other federal investments in understanding epilepsy genetics and channelopathies, cataloging gene variants, and sequencing individuals with epilepsy have increased our understanding of mechanisms across many rare epilepsies. However, the RELA analysis confirmed advances in molecular understanding of 38/44 rare epilepsies without associated translation to cures or interventions.

Addressing the infrastructure impediments goes beyond the capacity of this editorial and author. At base, NINDS has a broad mandate with more than 600 neurological disorders in its portfolio. It focuses a majority of effort on a small number of neurological disorders that impact millions of people.[28] Although NINDS is deeply committed to finding treatments for rare diseases, a third of which are thought to include a neurological component, the rare epilepsies are among a growing number of rare diseases in a large portfolio with limited bandwidth and resources.[29] Additionally, federal[30]and private investment in the epilepsies significantly lags behind funding for other disorders including

[24] https://www.epilepsy.com/make-difference/epilepsy-learning-healthcare-system-elhs [accessed June 18, 2020].

[25] https://phs.weill.cornell.edu/research-collaboration/research-programs/pediatric-epilepsy-learning-healthcare-system.

[26] N. Tian, J.B. Croft, R. Kobau, et al., CDC-supported epilepsy surveillance and epidemiologic studies: A review of progress since 1994, Epilepsy & Behavior, https://doi.org/10.1016/j.yebeh.2020.107123.

[27] Begle, C.E. & Durgin, T.L. (2015). The direct cost of epilepsy to the United States: A Systemic review of the estimates. Epilepsia, 56(9), 1376–87. https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13084.

[28] Rare Disease Research at NINDS, Director's Message, https://www.ninds.nih.gov/News-Events/Directors-Messages/All-Directors-Messages/Rare-Disease-Research-NINDS.

[29] https://www.ninds.nih.gov/News-Events/Directors-Messages/All-Directors-Messages/Rare-Disease-Research-NINDS.

[30] K.J. Meador, J. French, D.W. Loring, P.B. Pennell Disparities in NIH funding for epilepsy research. Neurology, 77 (2011), pp. 1305–1307; https://report.nih.gov/categorical_spending.aspx.

autism, Parkinson's disease, and Alzheimer's disease.[31] Moreover, according to Interagency Collaborative to Advance Research in Epilepsy (ICARE) – which evaluates epilepsy research across NIH Institutes – most funded epilepsy research is basic around disease mechanism with less money invested in translational and clinical research.[32] ICARE further found funding for structured training in epilepsy research is a small percentage of overall funding.[33] ICARE reported that less than 10% of epilepsy funding was dedicated to the 2012 Institute of Medicine Recommendations. A broad spectrum disease, a large portfolio, less funding for epilepsy research compared with other diseases, and funding within epilepsy out of sync with priorities all contribute to the challenge of translating research into cures or meaningful interventions in a time that matters to patients and their families.

There are reasons to be optimistic. While historically, epilepsy therapies have been narrowly focused on seizure control, opportunities are emerging especially among the rare genetic epilepsies to modify and potentially prevent and/or cure epilepsies. Moreover, the potential to apply learnings from rare epilepsies to other neurological diseases is high. For example, knowledge about the mTOR pathway in tuberous sclerosis complex may provide insights into head injuries with commonalities along the same pathway. Similarly, research across rare epilepsies designated as channelopathies caused by pathogenic variants in genes like KCNQ2 and SCN1A may increase our ability to recognize and diagnose other inherited neurological diseases. Epilepsy is uniquely positioned to capitalize on research advances and opportunities ripe for translation to patients, but we need systemic changes to training, funding, and strategizing to realize the promise. Further, we need to diversify our funding sources and explore innovative public and private partnerships to supplement and stimulate existing investments to eliminate our reliance on any single source.

4. Ready & raring for change

Although the landscape of The Epilepsies has changed dramatically over the past two decades, the systems for care, surveillance, and funding have not similarly evolved. A strong and growing collaborative movement is afoot led by impassioned, motivated, and resourceful advocates who are not only working diligently to educate patients and professionals, connect communities, and push research forward in their own disease, but they are doing this across diseases, shared comorbidities, and concerns. The strong response to the RELA survey further evidenced the climate change and the desire to address challenges through collaboration. When epilepsy thought leaders from around the world gather in January 2021 for the Curing Epilepsies meeting to set new research benchmarks and identify priority areas for transformative research in epilepsy, it is time to address the outdated infrastructure to catapult The Epilepsies into the 21st Century. The Rares are ready partners and RARing for change!

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[31] State of Research in The Epilepsies 2013, CURE, https://24ai3c1jd4ue1g13v835089r-wpengine.netdna-ssl.com/wp-content/uploads/2017/02/CCC-Whitepaper-State-of-Epilepsy.pdf [accessed June 18, 2020].
[32] ICARE, Slide 7.
[33] ICARE, Slide 5.